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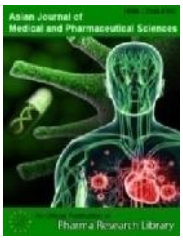

Review Article **Open Access**

Adverse Drug Reaction in Diabetes

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A B S T R A C T

Adverse drug reactions occur almost daily in health care institutions and can adversely affect a patient's quality of life, often causing considerable morbidity and mortality. Exenatide has a favorable safety profile, with adverse events of dizziness, headache and gastrointestinal discomfort. Incretin mimetics is being investigated to determine whether it is linked to acute pancreatitis and thyroid cancer. , hypoglycemia is a notable adverse event that can occur with the sulfonylurea class of drugs. There are conflicting data on whether the sulfonylurea class increases the risk of cardiovascular events there are conflicting data on whether the sulfonylurea class increases the risk of cardiovascular events, and further research is needed.

Keywords: Incretin mimetics, Hypoglycemia, Pancreatitis.

A R T I C L E I N F O

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1. Introduction

An adverse drug reaction (ADR) is an unwanted, undesirable effect of a medication that occurs during usual clinical use. Adverse drug reactions occur almost daily in health care institutions and can adversely affect a patient's quality of life, often causing considerable morbidity and mortality. Much attention has been given to identifying the patient populations most at risk, the drugs most commonly responsible, and the potential causes of ADRs. number of older adult who have type 2 diabetes mellitus. Older adults with diabetes often will be taking many other medications. Health care professionals who coordinate care for older patients with diabetes must not only be able to treat

hyperglycemia to target individualized goals of care but also anticipate and recognize the adverse effects of various pharmacologic agents prescribed.

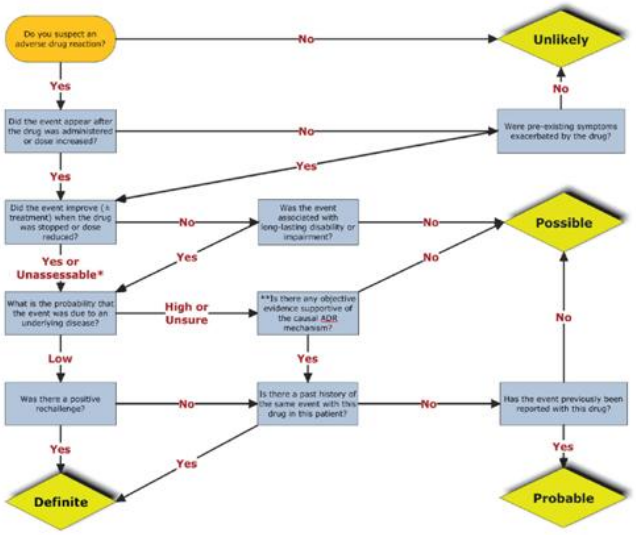

Figure 1: Causality tool of Adverse Drug Reactions.

Adverse drug reaction (ADR) monitoring and reporting activity is in its infancy in India. The important reason is lack of awareness and lack of interest of healthcare professionals in ADR reporting and documentation. A study conducted to determine the level of awareness of physicians about ADR and the extent of their involvement in pharmacovigilance activities showed that despite good observation and knowledge of ADR among physicians the rate of ADRs reporting and documentation is very low.

Therefore, this study was aimed to identify ADRs and assess their causality, preventability and severity, and also their risk factors in Indian ambulatory elderly patients. Prescriber knowledge about drug pharmacodynamics and pharmacokinetics and their interaction with normally aging physiology is critical in treating the elderly patient with diabetes. This knowledge is needed to minimize and even avoid the potentially adverse effects of hypoglycemia and the side effects associated with polypharmacy. When medications become necessary to the management of diabetes in an older patient, informed practitioners can correctly and safely write a prescription for the proper drug, dose and frequency.

According to the ADA recommendation changes in 1997, the fasting glucose concentration should be used in routine screening for diabetes as well as epidemiological studies; the threshold for fasting glucose was changed from 7.8 mmol/L (140 mg/dl) to 7.0 mmol/L (126 mg/dl); however the 2-h glucose criterion remains as = 11.1 mmol/L (200 mg/dL). For the diagnosis of diabetes, at least one criteria must apply: Symptoms of diabetes (polyurea, polydipsia, unexplained weight loss, etc) as well as casual plasma glucose concentration = 11.1 mmol/L (200 mg/dL). Fasting plasma glucose = 7.0 mmol/L (126 mg/dL), with no caloric intake for at least 8 h. 2-h plasma glucose = 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test (OGTT), with the glucose load containing 75 g anhydrous glucose in water.

2. Pharmacotherapy

- The aim of the treatment is primarily to save life and all eviate symptoms. Secondary aims are to prevent longterm
- Diabetic complications and, by eliminating various risk factors, to increase longevity. The first aim is not difficult to
- attain and in some elderly patients or those who lack motivation it is the only aim.58 The care of diabetes on selfmanagement is based on the patient's clinical status and his/her ability to participate in self-care. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Oral hypoglycaemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidenediones. The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and in adequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes.
- Diet and lifestyle strategies are to reduce weight, improve glycaemic control and reduce the risk of cardiovascular
- complications, which account for 70% to 80% of deaths among those with diabetes.59 Diabetes is best controlled
- Either by diet alone and exercise (non-pharmacological), or diet with herbal or oral hypoglycaemic agents or insulin (pharmacological).

Non-pharmacological interventions in the treatment of type 2 Diabetes Mellitus

- It has been shown that weight reduction and an increase in daily energy expenditure decrease insulin resistance and
- increase glucose tolerance.50 In fact, advice on diet and exercise are an important part of the treatment of type 2 DM. Overweight patients are advised to restrict calorie intake, consume food with low total fat content (especially
- Saturated fat) and high (predominately unrefined) carbohydrate content.

Diet and exercise

- Primary prevention is the main aim at preventing diabetes from occurring in susceptible individuals or in general population. Regular physical activity is an important component of the prevention and management of type 2

- diabetes mellitus. Prospective cohort studies have shown that increased physical activity, independently of other risk
- factors, has a protective effect against the development of type 2 diabetes.60-62 These epidemiological prospective
- studies demonstrated that various levels of regular physical activity one to several times a week were associated with a decrease incidence of the disease at long-term follow-up (4 and 5 years, respectively) in both men and women of
- Different age groups.60-62 Type 2 diabetes individuals with moderate or high aerobic fitness have long-term mortality 50-60% lower than diabetic individuals with low cardiorespiratory fitness.
- In type 1 diabetics, most studies have not found any benefit from exercise because of the likelihood of type 1 diabetics to consume additional carbohydrates in an effort to prevent hypoglycaemia. Again in type 1 diabetics, hypoglycaemia often develops during light to moderate exercise unless the insulin dose is reduced or extra carbohydrate consumed. In contrast, during and after brief, maximal-intensity exercise, glucose production increases much mo re than glucose disposal, resulting in hyperglycaemia even in non-diabetic individuals. In type 1 diabetic individuals, insulin levels cannot increase physiologically in response to this hyperglycaemia, so the hyperglycaemia is more marked and prolonged than in non-diabetic subjects. Nevertheless, type 1 diabetics who exercise regularly have marked lower long-term morbidity and mortality compared to their sedentary counterparts. For both type 1 and type 2 diabetic patients physical activity is accompanied by gains as well as risks. The physical hazards are generally higher and the metabolic benefits lower in the type 1 than in the type 2 diabetics. On the other hand, for psychological and social reasons, physical activity is desirable because most type 1 diabetic patients are younger than their type 2 counterparts.

Treatment of hypoglycaemia

- Initially glucose 10-20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps.
- Hypoglycaemia which causes unconsciousness is an emergency. *Glucagon* can be given for acute insulin-induced hypoglycaemia; it is not appropriate for chronic hypoglycaemia. It is given at a dose of 1 mg (1 unit) by intramuscular, subcutaneous and intravenous in circumstances when an intravenous glucose would be difficult or impossible to administer. If not effective within 10 min, give intravenous glucose.
- Alternatively, 50 ml of 20% glucose infusion may be given intravenously into a large vein
- Through a large gauge needle. Care should be taken to see that it does not cause extravasation since it is an irritant at this concentration. Alternatively, 25 ml of 50% glucose intravenous infusion may be given,
- Though this concentration is viscous and difficult to administer. Glucose at a
- Concentration of 10 % can be given but a large volume is required.
- Hypoglycaemia caused by oral hypoglycaemic agents should be transferred to a hospital since the hypoglycaemic effects may persist for many hours.

Newer Agents for the Treatment of Diabetes Mellitus

- Potential new antidiabetic agents and compounds are undergoing clinical trials such as
- *a-Glucosidase* inhibitors such as *voglibose* have already been mentioned earlier. It reduces the
- Postprandial increase in glycaemia similar to acarbose and miglitol.
- *a-Amylase* inhibitors like acarbose are weak inhibitors of a-amylase activity, but attempts to
- Specifically inhibit a-amylase activity have not been successful.
- Novel insulins. *Thyroxyl-insulin*, an insulin linked to thyroxine, is highly bound to plasma proteins via
- its thyroxyl moiety, ensuring a prolonged plasma half-life and limited transport across the
- endothelium, but has free access to hepatocytes. Others like insulin initiators and potentiators act by enhancing the effect of glucose and other nutrient initiators for example agents that increase cellular concentration of cyclic adenosine monophosphate (cAMP).

A lot of attention has recently been focused on the therapeutic potential of glucagon-like peptide(GLP-1) and glucose-dependent insulinotropic peptide (GIP).222 In the presence of stimulatory concentration of glucose, GLP-1 is a potent insulin secretagogue in non-diabetic subjects, subjects with impaired glucose tolerance (IGT), and type 2 diabetic subjects.222 In acute and chronic studies, injection or infusion of GLP-1 before or during meals reduced postprandial hyperglycaemia and improved glycaemic control without causing clinical hypoglycaemia.222 The main limitation to therapeutic application of GLP-1 has been its very short plasma half-life of less than two min after intravenous injection and 1 h after subcutaneous injection.222 This is due to its rapid degradation at the N-terminal by the circulating enzyme dipeptidyl peptidase 4 (DPP-4).222 Hence an analogue of GLP-1 that modify the amino acid sequence to avoid degradation has been developed; exendin-4 is such a product, that was first isolated from a North American Reptile known as the Gila monster (*Heloderma suspectum*). Exendin-4 has a longer half-life than native GLP-1, but retains the same biological profile. *GIP* stimulates insulin biosynthesis and contributes substantially to the overall incretin response,

- However, GIP may raise postprandial glucagon. *Dipeptidyl peptidase 4* (DPP-4) degrades a variety

- of circulating peptides (e.g. PYY and NPY) including glucagon, which might contribute to its
- Glucose-lowering effect, but it is not yet evident whether the effects of DPP-4 inhibitors on other peptides could limit their use.

3. Adverse Drug Reactions

The most common and one of the most devastating side effects of pharmacologic treatment of older patients is hypoglycemia. The risk of severe or fatal hypoglycemia exponentially increases with age. The landmark trial Action to Control Cardiovascular Risk in Diabetes, or ACCORD, was discontinued early when interim results indicated a statistically significant increase in mortality in patients who received intensive therapy with the goal of achieving a glycated hemoglobin level of 6% or less. Further analysis of data from this trial showed that individuals in this group used more medication and had more hypoglycemic events, greater weight gain and greater fluid retention than individuals in the group that received standard therapy with the goal of a glycated hemoglobin level of 7% to 7.9%. Although the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, or ADVANCE trial, which similarly compared intensive blood sugar control to standard therapy, did not show a difference in mortality between the two groups, it did demonstrate an increase in the number of hypoglycemic events and hospitalization in those who were more intensively treated.

In light of these findings, the American Diabetes Association has recommended that goals be individualized, with more flexible goals for older adults, those with advanced disease and complications or those with limited life expectancy. Older patients also may experience delayed psychomotor responses as a result of interventions designed to correct hypoglycemia. Glucagon, one of the main counter-regulatory responses to hypoglycemia, is impaired in older people and, to a greater extent, older patients with diabetes. Altered psychomotor and impaired counter-regulatory responses must be balanced with the functional and cognitive status of the individual In addition to being aware of and recognizing hypoglycemia, patients must be able to access food or drink to reverse this iatrogenic condition.

Hypoglycemia manifests through an easily recognizable adrenergic constellation of symptoms, most notably tremor, sweats or weakness. However, older patients commonly demonstrate a primarily neuroglycopenic syndrome (i.e., confusion, delirium, dizziness and falls) that can be misdiagnosed as a neurologic event such as a transient ischemic attack or syncope. Listed below are some common classes of medications prescribed for diabetes. Although this is not a comprehensive list of medications and corresponding adverse events, notes are provided on the potential for adverse reactions in this population. Clear provider instructions and patient (or caregiver) comprehension are essential to ensure directed drug dosing, timing and administration.

Commonly prescribed medications

Thiazolidinediones: Adverse events associated with the thiazolidinediones are weight gain, edema, macular edema, congestive heart failure, increased bone fracture risk and, when combined with other diabetic medications, hypoglycemia. Of notable mention are several studies that suggest the potential for adverse cardiovascular events with rosiglitazone and potential for benefits in cardiovascular risk reduction from pioglitazone. Further studies are needed regarding these events and how they affect the older population with diabetes. Ongoing concerns about fluid retention limit the utility of these studies for older patients with diabetes.

Biguanide

Patients will commonly experience gastrointestinal side effects that tend to improve after the first few weeks of treatment with metformin. Metformin should not be used in individuals older than age 80 until renal function has been established. Lactic acidosis is a potential side effect of metformin, yet evidence is scant that it will occur with contraindications to metformin. The biguanide class is also contraindicated in patients with renal disease, renal dysfunction or abnormal creatinine clearance rates.

Sulfonylureas

As previously mentioned, hypoglycemia is a notable adverse event that can occur with the sulfonylurea class of drugs. There are conflicting data on whether the sulfonylurea class increases the risk of cardiovascular events, and further research is needed. Older patients should be instructed about the potential for weight gain as more insulin is produced and glucose is utilized.

Meglitinides

Weight gain is a common feature of this class that includes the medications repaglinide and nateglinide. Although hypoglycemia is a possible side effect, mealtime dosing of meglitinides enables older patients to be flexible with their dosing schedule. Repaglinide may also be a good choice for an older patient or a patient with renal disease, as 90% of the drug can be recovered in the feces.

Insulin therapy

Insulin is often an underutilized therapeutic modality in the older patient with diabetes because of the practitioner's, patient's or family's concerns about administration and the risk of hypoglycemia.26 Weight gain is another common adverse effect of insulin products. Patients should be appropriately educated on the proper administration, dosing and effects of the various insulin products. Visual and cognitive acuity should be assessed prior to initiating and tailoring products to ensure that patients can easily administer the amount of insulin prescribed. Specifically, the use of insulin pens can greatly assist older adults who may have issues with vision or dexterity.

In some of the pens the correct dose can be achieved even with clicks of the pen, ensuring more accurate dosing. With the advent of long-acting, oncedaily- administered insulin formulations, capable and willing caregivers can often assist the older individual with this pharmacologic intervention.

Polypharmacy: The administration of multiple pharmaceutical products in concert (known as

polypharmacy) may potentiate or decrease the effects of common diabetes medications in the older population. Such patients commonly have other systemic, related chronic conditions; the physician must recognize the variety of medications the patient may be taking and the potential interactions among these medications. In one study of 18,968 patients with diabetes, at least 16% were dispensed a medicine that is associated with adverse interactions, and 22.7% were dispensed at least one potentially inappropriate medicine. Every six to 12 months, physicians should request that their older patients bring their medications with them to their appointments as an audit for usage and also as an educational opportunity. This "brown bag" medication review is one method to avert potential polypharmacy. Physicians should also strive to partner with family members who are often caregivers for these patients.

Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, has a favorable safety profile, and a low incidence of hypoglycemia. Nausea generally resolves with dosing strategies during the introduction of the medication. Sitagliptin is being investigated to determine whether it is linked to acute pancreatitis. Abdominal pain and substantially decreased appetite should be cause to discontinue this medication. Saxagliptin has a similar adverse effect profile but is associated with a decrease in the absolute lymphocyte count (this was not observed at the 2.5 mg dose). Although the clinical importance of this laboratory finding has not been firmly established, saxagliptin has been associated with an increased number of upper respiratory infections, as well as urinary tract infections. Repeated infections should prompt a review of saxagliptin's clinical utility in the individual's case. Despite an increased financial burden for the elderly, DPP-4 inhibitors may be particularly useful in older adults, since they exhibit few drug-to-drug interactions. In addition, these medications can be used in adults with all stages of renal disease, including end-stage renal disease (but dosage adjustment is needed).

Incretin mimetics

Exenatide has a favorable safety profile, with adverse events of dizziness, headache and gastrointestinal discomfort. Incretin mimetics is being investigated to determine whether it is linked to acute pancreatitis and thyroid cancer. Liraglutide has a similar safety concern but carries the benefit of once daily dosing administered in a pre-filled pen. Since weight loss can be substantial in patients using this medication, the role of incretin mimetics is limited in the vulnerable or frail elderly population.

4. Conclusion

As aging is a risk factor for chronic care conditions such as diabetes, physicians are faced with a growing population of older patients with this disorder. Adverse events associated with the thiazolidinediones are weight gain, edema, macular edema, congestive heart failure, increased bone fracture risk and, when combined with other diabetic medications, hypoglycemia. Ensuring that patients are educated on both their medications and potential adverse events is a necessity in every care plan to limit potential treatment complications. Oral hypoglycaemic agents are also useful in the treatment of type 2 DM. Oral hypoglycaemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidenediones. The main objective of these drugs is to correct the underlying metabolic disorder, such as insulin resistance and in adequate insulin secretion. They should be prescribed in combination with an appropriate diet and lifestyle changes.

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